

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 026 090
A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 80303293.7

(51) Int. Cl.³: **C 01 B 25/32**
C 04 B 35/00, A 61 F 1/00

(22) Date of filing: 18.09.80

(30) Priority: 25.09.79 JP 123000/79

(43) Date of publication of application:
01.04.81 Bulletin 81/13

(84) Designated Contracting States:
DE FR GB IT NL

(71) Applicant: KUREHA KAGAKU KOGYO KABUSHIKI
KAISHA
9-11 Horidome-cho 1-chome Nihonbashi Chuo-ku
Tokyo(JP)

(72) Inventor: Nagai, Hiroshi
4-2-47, Fujimi-cho Chofu-shi
Tokyo(JP)

(72) Inventor: Nishimura, Yasushi No. 404
Haitsu-Takada-No-Baba
116-11 Takada-No-Baba 1-chome
Shinjuku-ku Tokyo(JP)

(74) Representative: Myerscough, Philip Boyd et al,
J.A.Kemp & Co. 14, South Square Gray's Inn
London, WC1R 5EU(GB)

(54) Process for preparing hydroxyapatite, and filter cake, ceramic material and implant material comprising hydroxyapatite.

(57) Hydroxyapatite is an inorganic component of skeletal tissues, such as bones and teeth. It is known to synthesise hydroxyapatite for use as implant materials, such as artificial bones, by the reaction of calcium hydroxide with phosphoric acid. Known synthetic hydroxyapatite is, however, not sufficiently like the naturally occurring material to be entirely satisfactory for use in providing implant materials.

The invention provides a process for synthesising hydroxyapatite which comprises thermally decomposing calcium carbonate, cooling the resultant calcium oxide, slaking the cooled calcium oxide, and reacting the resulting calcium hydroxide with phosphoric acid. A filter cake of the synthetic hydroxyapatite thus produced is porous and contains crystals which can readily be sintered to provide a thermally stable ceramic material which is colorless or semi-transparent and useful in providing implant materials compatible with a living body.

EP 0 026 090 A2

- 1 -

DESCRIPTION

"PROCESS FOR PREPARING HYDROXYAPATITE, AND FILTER CAKE,
CERAMIC MATERIAL AND IMPLANT MATERIAL COMPRISING
HYDROXYAPATITE"

The present invention relates to a process for preparing hydroxyapatite, and to a filter cake, ceramic material or implant material comprising hydroxyapatite. The present invention is primarily concerned with providing
5 a colourless and translucent ceramic material of hydroxyapatite having a high density, a high purity and a high thermal stability, which is useful in implant materials comprising a ceramic material and an organic binding material.

10 Hydroxyapatite is represented by the formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ or $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$, and is an inorganic component of the hard tissues of living bodies such as bones, and teeth.

It is known that sintered synthetic hydroxy-
15 apatite (hereinafter referred to as a ceramic hydroxy-apatite material) is usable as an implant material, such as an artificial dental root or artificial bone (for instance, see Aoki and Kato, "Ceramic", 10(7) : 469 (1975)). Clearly a ceramic hydroxyapatite material should
20 resemble naturally occurring hydroxyapatite in its physical properties. Thus, a ceramic hydroxyapatite material for use in a living body should be colourless, have a high density and purity and be safe to use.

A pure ceramic material should not contain, as
25 far as possible, elements other than Ca, P, O (as PO_4) and H (as OH), the elemental components of hydroxyapatite; its Ca/P atomic ratio should be close to 1.67/1 which is the theoretical value of hydroxyapatite and the physical structure should be as close as possible to that of pure
30 hydroxyapatite. Defects in the physical structure of a ceramic material, if any, can be detected by X-ray analysis

- 2 -

or by treating a specimen at a high temperature of about 1350°C. The latter method, as will subsequently be explained in more detail, readily detects the presence of an impurity which is frequently contained in a synthetic ceramic hydroxyapatite material, namely whitlockite which has a lower Ca/P value and a different physical structure than natural hydroxyapatite and is highly soluble in aqueous solvents.

The presence of impurities and structural defects in a synthetic ceramic material makes the material coloured and the impurities tend to be eluted within a living body containing an implant of the synthetic material. According to one viewpoint, it may be preferable to have an accelerated elution of impurities within the tissues of the living body, but from the viewpoint of safety, there may be unfavorable effects on the living body due to topical electrolyte imbalance or harmful action of an impurity upon such elution.

Accordingly, there is a need for a synthetic ceramic hydroxyapatite material that is highly pure, almost colourless and of high density. However, as will be explained below, a synthetic ceramic material satisfying such demands had not previously been known.

A number of processes for synthesizing hydroxyapatite have been proposed, for instance, by R.W.Mooney, et al., "Chem. Rev.", 61:433(1961) and by Kanazawa, et al., "Kagaku no Ryoiki", 27:622(1973). However, there are few disclosures of the preparation of a ceramic material by the firing of a synthetic hydroxyapatite. Monreo has reported that he obtained a ceramic material by compression-molding powdery hydroxyapatite and firing the molded material at a temperature of 1300°C under normal pressure (refer to "J. Dent. Res.", 50,860(1971)), but since his ceramic material contains as much as 30% by weight of whitlockite (alpha-calcium triphosphate), it

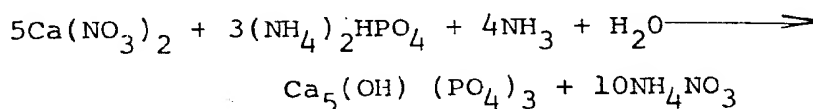


- 3 -

cannot be said that his ceramic material is of highly pure hydroxyapatite.

A reason why a ceramic material of highly pure hydroxyapatite has not been available is considered to be the fact that the hydroxyapatite used for making the ceramic material did not have the correct stoichiometrical composition or it had some structural defects resulting in the by-production of whitlockite at the time of firing. To test this, a trial has been carried out wherein hydroxyapatite of the correct stoichiometric composition was synthesized and then the hydroxyapatite was fired. However, the hydroxyapatite synthesised by the conventional process was difficult to sinter and of poor thermal stability due to problems with purity and crystalline structure. Accordingly, a thermally stable ceramic material with a high density and a high purity has not yet been obtained. For instance, although Japanese Laid Open Patent Application No. 64199/77 offers a method of adding compounds such as MgO in order to improve the insufficient sintering property of a synthetic hydroxyapatite, this method is based on the introduction of elements other than Ca, P, O and H and so cannot provide a highly pure ceramic hydroxyapatite material.

In a different approach, M. Jarcho used a method by Haek (refer to Angew. Chem., 67:327 (1955) and Inorg. Synt., 7:63 (1963)) based on the following reaction:



in which calcium nitrate is reacted with diammonium hydrogen phosphate while regulating the pH of the reaction system at 10 to 12 by the addition of ammonia to synthesize hydroxyapatite. The cake-like hydroxyapatite obtained by filtrating the reaction mixture can then be fired at a temperature of 1100 to 1200°C to provide a

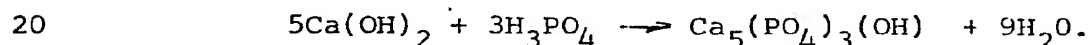


- 4 -

ceramic material.

It has been reported that a ceramic hydroxyapatite material having a mean crystal size of 0.2 to 3 microns and a density of 3.10 to 3.14 g/cm³ was
5 obtained by this procedure (refer to U.S. Pat. No. 4,097,935, Japanese Patent Applications Nos. 40400/76, 94309/77 and "J. Material Sci.", 11:2027(1976)). However, it is disclosed in this literature that the ceramic hydroxyapatite material was partially decomposed to a
10 by-product, whitlockite, when treated at a temperature above 1250°C for more than one hour. That is, the ceramic hydroxyapatite material obtained by the above-mentioned procedure is structurally unstable and accordingly has poor thermal stability. In addition, there is the
15 difficulty of having to remove the ammonium nitrate by-product.

A different method for synthesizing hydroxyapatite utilizes the reaction of calcium hydroxide with phosphoric acid:-



This reaction could develop into an industrial method for producing hydroxyapatite because (1) no impurities are introduced and (2) only water is formed as a by-product, but Mooney has said ("Chem. Rev.",
25 61,433(1961)) that it is difficult to obtain hydroxyapatite of the correct stoichiometric composition (theoretical Ca/P atomic ratio of 1.67:1) by the reaction, and that only hydroxyapatite having a Ca/P ratio of 1.50:1 corresponding to calcium triphosphate is obtainable. On
30 the other hand, R. Wallaëys (refer to "Angew. Chem. (Paris)", 7,808 (1952)) obtained a hydroxyapatite having a Ca/P atomic ratio of 1.61:1 to 1.67:1 by boiling the reaction mixture after the reaction was over in order to make the reaction proceed completely or making the reaction
35 proceed to the neutral point to phenolphthalein while



- 5 -

boiling.

However, the results of experiments on the method of Wallaey's carried out by the inventors of the present invention have shown that a dried filter cake
5 of hydroxyapatite obtained by the Wallaey's method has a poor sintering property so that a ceramic material having a density of only about 3.11 g/cm^3 is obtained even by the hot-press method at a high temperature and, moreover, the ceramic material is coloured blue. The
10 cause of the blue colouring is not yet known, but may be due to some structural defect and/or to the presence of a minute amount of impurities.

The inventors of the present invention have studied the relationship between the sintering property
15 or the thermal stability of the ceramic material and the crystalline form and shape and the structure of synthetic hydroxyapatite, and have found that a ceramic material of excellent thermal stability, colour, purity and strength which has no structural defects and which does not
20 decompose to form whitlockite even upon heating for one hour at a temperature of 1350°C is obtained by firing a dried filter cake of a synthetic hydroxyapatite prepared in a particular manner.

The invention provides a process for preparing
25 hydroxyapatite, which comprises the steps of,

- (a) converting calcium carbonate powder into calcium oxide by thermal decomposition in an inert atmosphere at a temperature of 800 to 1300°C for 0.5 to 10 hours;
- 30 (b) cooling the calcium oxide to a temperature lower than 500°C in the inert atmosphere to obtain extremely porous highly reactive calcium oxide;
- (c) slaking the cooled calcium oxide with water while agitating thereby to obtain a fine calcium
35 hydroxide milk of high purity; and

- 6 -

(d) reacting the calcium hydroxide with an aqueous solution of phosphoric acid while agitating in an inert atmosphere, thereby to obtain hydroxyapatite.

5 In the process of the present invention an aqueous suspension of minute particles of calcium hydroxide is formed in step (c) by bringing porous and minute particles of practically pure calcium oxide into reaction with an excess amount of water and when this calcium hydroxide is reacted in step (d) with an aqueous
10 solution of phosphoric acid a milky reaction mixture containing the reaction product, a highly pure hydroxyapatite, is obtained.

The milky reaction mixture can then be filtered, the separated cake washed with water and dried to provide
15 an aggregate of hydroxyapatite having the following properties:

Atomic ratio of Ca/P: 1.67:1 to 1.69:1,
Mean dimensions of hydroxyapatite crystals
length : 150 to 1200 Å
20 width : 50 to 400 Å, and
length/width ratio : 3:1 to 10:1
Pore volume : 0.2 to 0.8 cm³/g
Mean pore-radius : 50 to 150 Å.

By firing the dried filter cake, the aggregate
25 of hydroxyapatite, a ceramic material of hydroxyapatite is obtained which is colourless or semi-transparent and has the following physical properties:-

Atomic ratio of Ca/P : 1.67:1 to 1.69:1,
Mean crystal size : 4 to 20 microns, and
30 Density : 3.14 to 3.16 g/cm³.

The mean crystal size of this ceramic material is larger than that of known synthetic ceramic hydroxyapatite materials which indicates that the ceramic material of the present invention is prepared from purer
35 raw materials than those used for preparing the known materials. In addition, the ceramic material of the

- 7 -

invention has a thermal stability such that substantially no whitlockite is formed upon heating for at least one hour at 1350°C and this indicates that the ceramic material is substantially free of structural defects.

The invention will now be described in more detail:

Porous and minute particles of calcium oxide for use in the process of the present invention are obtained in step (a) of the process by thermally decomposing calcium carbonate powder. The calcium carbonate is preferably of high purity, say higher than 99.0%, preferably 99.8% or more, and in a micro-fine state. The conditions of the thermal decomposition of the calcium carbonate are: in an inert atmosphere, at a temperature of 800 to 1300°C, preferably 950 to 1200°C, for 0.5 to 10 hours, preferably one to five hours. Upon decomposition under the above-mentioned conditions, calcium carbonate is converted to a highly porous and reactive fine powder of calcium oxide while gaseous carbon dioxide is evolved.

If milder conditions of thermal decomposition were to be employed undecomposed calcium carbonate would remain in the calcium oxide produced. Not only is it difficult to remove any remaining calcium carbonate from the calcium oxide, but also any remaining calcium carbonate would cause structural defects and a reduction in the thermal stability of a ceramic hydroxyapatite material. If, however, the conditions of the thermal decomposition are more severe or if the product of the thermal decomposition were not cooled in step (b) in an inert atmosphere until the temperature of the product has fallen to 500°C, preferably to 200°C, the porosity and the reactivity of the calcium oxide produced would be impaired. The inert



- 8 -

atmosphere for steps (a) and (b) should be an atmosphere which does not contain any components, such as gaseous carbon dioxide and ammonia, inducing a secondary reaction with the calcium oxide produced or with calcium hydroxide. It is effective to blow an inert gas such as nitrogen, helium or argon through the thermal decomposition zone in order to obtain the inert atmosphere because gaseous carbon dioxide generated is thus removed from the system.

An aqueous suspension of minute particles of calcium hydroxide is produced in step (c) by adding the calcium oxide from step (b) to a large amount of water with high speed stirring to provide turbulent flow under an inert atmosphere. The amount of water to be used should be at least enough to slake the calcium oxide but is not otherwise limited, however it usually is 10 to 100 parts by weight per part by weight of calcium oxide.

The slaking reaction is carried out with high speed stirring, preferably at a relatively low temperature for a relatively long time period and usually at 0 to 80°C, preferably 0 to 50°C, for 0.5 to 96 hours, preferably 1 to 24 hours.

The end point of the slaking reaction can be determined by X-ray diffraction analysis, wherein a part of the reaction product is withdrawn as a specimen and the disappearance of a d_{200} line in the X-ray diffraction pattern of the specimen is taken as a sign that the reaction is complete.

The mean particle size of the calcium hydroxide resulting from step (c) of the process of the present invention is 0.05 to 0.1 micron and is far smaller than the mean particle size of one to ten microns of calcium hydroxide obtained by dispersing commercial calcium hydroxide in water.

- 10 -

sedimentability and is easily separable by filtration. The synthetic hydroxyapatite crystals are, as has been described, 50 to 400 Å in width and 150 to 1200 Å in length, and have a length to width ratio of 3 to 10.

5 These dimensions are clearly unlike those of the plate-like crystals about 200 Å in width and about 200 Å in length obtained by the aforementioned reaction between calcium nitrate and diammonium hydrogen phosphate. The easy sedimentability of the synthetic hydroxyapatite
10 obtained by the process of the present invention is considered to be due to such a size of crystals, their shape and form and further to the state of electric charge on the surface of the crystals. Moreover, these factors presumably contribute to the formation of the
15 aggregate, or filter cake, of hydroxyapatite of the present invention, which has a favorable sintering property.

An aggregate of hydroxyapatite according to the present invention is obtained by filtering the
20 synthetic hydroxyapatite obtained by the above-mentioned process, suitably to a water content of 0 to 2% by weight. The thus obtained filter cake or aggregate of hydroxyapatite has a pore volume of 0.2 to 0.8 cm³/g and pore radius of 50 to 150 Å, and
25 comprises hydroxyapatite crystals having a Ca/P atomic ratio of 1.67:1 to 1.69:1, crystal size of 50 to 400 Å in width, 150 to 1200 Å in length, and width to length ratio of 3:1 to 10:1, and these properties affect the specific properties of the ceramic
30 hydroxyapatite material.

The aggregate of hydroxyapatite according to the present invention has a favorable sintering property and when fired as it is, a ceramic material having excellent properties is obtained.

35 Naturally, conventional methods for molding and



- 9 -

The suspension of fine particles of calcium hydroxide is an important requisite for obtaining hydroxyapatite with a favorable sintering property described later.

5 Synthetic hydroxyapatite is formed in step
(d) of the process of the present invention in a
milky state by adding an aqueous solution of phosphoric
acid in an amount corresponding to a Ca/P atomic ratio
of 1.67:1 to 1.69:1 to the aqueous suspension of
10 minute particles of calcium hydroxide under an inert
atmosphere. In the preparation of the hydroxyapatite,
it is preferable that high speed stirring is continued
after completing step (c) and that the aqueous solution
of phosphoric acid is added to the system with stirring.

15 The phosphoric acid is usually an aqueous one
to ten percent by weight solution and the solution is
slowly added to the calcium hydroxide suspension. In
this connection, the high speed stirring referred to
herein means stirring which causes turbulent flow of
20 the liquid in the reaction system.

The reaction temperature of step (d) suitably
is 0 to 50°C. At a lower temperature, the viscosity of
the suspension would be so high that a uniform reaction
would become difficult, while at a higher temperature
25 the sintering property of the aggregate of hydroxy-
apatite is impaired. Thus, the reaction temperature of
step (d) is an extremely important factor affecting the
size of crystals, concerning the sintering property,
or affecting the easily sedimenting property which will
30 be described later. The reaction is usually carried
out for 0.5 to 200 hours, preferably for 5 to 100 hours.
The reaction mixture is highly alkaline having a pH of
about 13 initially, falling to 8 to 9 at the completion
of the reaction.

35 Although the synthetic hydroxyapatite in the
reaction system assumes a milky state, it has excellent

- 11 -

firing the aggregate are applicable in preparing the ceramic material according to the present invention, for instance the aggregate may be molded using a metal or rubber mold and then baked, or the aggregate may be
5 molded and fired by a hot press method, or a molded cake can be fired under a reduced pressure.

A ceramic material which is highly translucent, highly pure, highly dense and highly stable thermally is obtainable by firing under reduced pressure after
10 pressure-molding an aggregate of hydroxyapatite according to the present invention. The conditions of firing suitably are a temperature of 850 to 1400°C, preferably 1250 to 1400°C, for 0.5 to 5 hours, preferably 1 to 3 hours. It has been noticed that the growth of the
15 hydroxyapatite crystals during the sintering by firing in accordance with the invention is remarkably greater than when conventional hydroxyapatite is fired. This is presumably due to the above-mentioned specific properties of the aggregate of hydroxyapatite and its
20 favorable sintering property.

The ceramic hydroxyapatite material prepared according to the present invention has the following properties of:

- 25 a) atomic ratio Ca/P : 1.67:1 to 1.69:1;
- b) mean size of crystals: 4 to 20 microns;
- c) density : 3.14 to 3.16 g/cm³,
and
- 30 d) thermal stability : no formation of
whitlockite detectable
after heating for one
hour at 1350°C.

While known ceramic hydroxyapatite materials form whitlockite when heated at a temperature higher than 1200°C or 1300°C, the ceramic material according
35 to the present invention is extremely stable at



- 12 -

temperatures higher than 1300°C, and the size of the crystals of the material according to the present invention is larger than that of the known ceramic hydroxyapatite materials, so that the former is clearly
5 different from the latter.

The ceramic material according to the present invention has excellent stability within a living body presumably due to the absence of structural defects.

The thermal stability of the above-mentioned
10 ceramic material is confirmed by the determination of X-ray diffraction pattern after sintering the material for one hour at a temperature of 1350°C.

The process of the present invention is extremely effective as an industrial method and can be used to
15 provide a ceramic hydroxyapatite material which is chemically and physico-structurally pure and stable enough to be used within living bodies and useful as an implant material such as artificial dental roots and artificial bones.

20 The practical application of the ceramic hydroxyapatite material as an implant material, particularly as an artificial dental root material, will next be described. The ceramic material may be solely utilised for an implant material.

25 An implant material according to the present invention is prepared, with consideration to processability, ease of handling and mechanical strength, by molding a mixture of the ceramic hydroxyapatite material having a particle size smaller than 1000
30 microns, preferably 0.01 to 100 microns, and an organic matrix, or by impregnating a porous ceramic material of the present invention with an organic bonding material. In preparing the implanting material, it is important that the ratio of the area of the hydroxyapatite phase at the
35 working surface (that is the surface which in use contacts bone) of the implant material to that of the organic

- 13 -

bonding material is 5 : 95 to 70 : 30, preferably 10 : 90 to 60 : 40. When the hydroxyapatite phase provides more than 70% of the surface area of the working surface, the adhesion of the implant to natural bone is too great so that the natural bone tends to be damaged when the implant is removed. However, when the hydroxyapatite phase provides less than 5% of the surface area of the working surface, the implant tends to be naturally rejected. The above-mentioned ratio has been decided in consideration of the durability and adhesiveness of an artificial dental root.

The organic bonding material should have a long active life if it is to be used in a long-term implant in a living body and should not degrade the cells of the living body. Bonding materials which may be used include polycondensates of bisphenol A and glycidyl methacrylate, methyl methacrylate polymers, 2-hydroxyethyl methacrylate polymers, triethyleneglycol dimethacrylate polymers, ethylene polymers, sulfone polymers, polyamides, polyesters, tetrafluoroethylene polymers, vinylidene fluoride polymers and polycarbonates. These materials can be used singly or as mixtures of two or more thereof. The polymers can be homopolymers, or copolymers of the appropriate monomer with one or more copolymerisable monomer.

In addition, the ceramic material of the present invention can be used as a component of a material to be used within a living body such as a co-existent-type sintered material with an organic substance such as cellulose or collagen, a porous material prepared by boring, a composition prepared by impregnating with an organic resin, or impregnating and polymerizing an organic monomer into the porous material, a composite of the powdery ceramic material with an organic or inorganic matrix, or a combination of these.



- 14 -

The hydroxyapatite according to the present invention can also be used as a filling material for a chromatographic column.

The present invention will be described in more detail by reference to the following Examples:

EXAMPLE 1

600 g of powdery calcium carbonate of reagent grade (G.R.) were introduced into an electric furnace under a flow of gaseous nitrogen supplied at a flow rate of one litre/min. and heated to a temperature of 1000°C at a rate of 3°C/min. After heating for 3 hours at 1000°C to decompose the calcium carbonate, the furnace was cooled to 200°C under the flow of gaseous nitrogen at a rate of one litre/min to provide 335 g of calcium oxide in a yield of 99.7%. It was confirmed by X-ray diffraction analysis that the calcium oxide did not contain calcium carbonate. The purity of the product determined by the EDTA-method was 99.8%. According to microscopical observation, the crystal shape of the obtained calcium oxide was similar to that of the raw material, calcium carbonate, and the crystal of the calcium oxide was porous.

Into a 17-litre three necked porcelain enamelled tank provided with a heater, a temperature-controller and a thermometer, 6 litres of de-aired distilled water were introduced, the atmosphere in the tank was substituted by nitrogen while agitating with a stirrer operating at 350 rpm. Then, 280 g (5 mol) of the calcium oxide were slowly added within 10 minutes, and then made to react for 5 hours at 50°C, and for 15 hours at room temperature under the atmosphere of gaseous nitrogen to obtain a suspension of calcium hydroxide of 0.075 micron in mean particle diameter.

Next, while keeping the suspension in turbulent flow by agitation at 3000 rpm, three moles of an aqueous 3.5% solution of phosphoric acid prepared from 85%

- 15 -

phosphoric acid, were added over 30 minutes, and then the reaction was continued for 48 hours at a temperature of 20°C. After the reaction was over, the resulting suspension was filtered under pressure and the residue
5 was washed with water and dried at 150°C for 16 hours.

Thus, 497 g of a dried filter cake of hydroxyapatite were obtained and named as Specimen No. 1. The properties of the dried material, that is the aggregate of a hydroxyapatite of the present invention,
10 are shown in Table 1.

EXAMPLE 2

Another aggregate of hydroxyapatite of the present invention named as Specimen No. 2 was prepared by the same procedure as in Example 1 except that the
15 reaction with phosphoric acid was carried out at 40°C for 24 hours as compared with 20°C and 48 hours in Example 1. The properties of Specimen No. 2 are also shown in Table 1.

COMPARATIVE EXAMPLE 1

20 An aqueous dispersion prepared by adding 5 mols of powdery calcium hydroxide of reagent grade (G.R.), into 6 litres of de-aired distilled water was introduced into the porcelain enamelled tank used in Example 1, and while agitating at 3000 rpm under the substituted nitrogen
25 atmosphere by a flow of gaseous nitrogen, 3 moles of an aqueous 3.5% solution of phosphoric acid were slowly added to the dispersion. After carrying out a reaction at a temperature of 70°C for 24 hours, the same procedures as in Example 1 were taken to obtain an
30 aggregate of hydroxyapatite named as Specimen No. 3, the properties of which are also shown in Table 1.

COMPARATIVE EXAMPLE 2

Another aggregate of hydroxyapatite named Specimen No. 4 was prepared by the following known
35 method and its properties were also shown in Table 1:

- 16 -

Diammonium hydrogen phosphate (160 g) was dissolved in distilled water (3 litres) and an aqueous 28% ammonia solution (1700 ml) was added to the solution to adjust the pH to 11 to 12. Distilled water was further added to it to dissolve the thus precipitated diammonium hydrogen phosphate. This solution was poured over 30 minutes into a solution prepared by dissolving 477 g of calcium nitrate in 188 ml of distilled water adjusted to pH of 12 by an addition of 60 ml of a concentrated aqueous ammonia solution and kept at a temperature of 20°C with high speed stirring. The mixture was further diluted with distilled water until the total volume was 7.0 litres. After boiling the thus diluted solution for 10 min, it was left at room temperature for 20 hours.

The thus produced gelatinous material was filtered using a Buchner funnel under slightly reduced pressure, washed with water while kept on the filter, and when cracks appeared on the surface of the filter cake, a higher vacuum was applied for 2 hours. The filter cake was dried at 150°C for 15 hours to provide 197 g of an aggregate of hydroxyapatite.

EXAMPLE 3

Respective specimens of the aggregates of hydroxyapatite obtained by Examples 1 and 2 and Comparative Examples 1 and 2 were placed in an electric furnace and heated to a temperature of 1350°C at a rate of 3°C/min. After keeping at that temperature for one hour, each specimen was removed from the furnace to be cooled to room temperature. The thus obtained ceramic materials had the respective properties shown in Table 2.

Samples of each ceramic material were crushed to pieces of about 5 mm in size, and after immersing the pieces in a 0.1% aqueous solution of neutral red at room temperature for 15 hours, the pieces were washed

- 17 -

with water and dried to examine the coloration of their crushed surfaces. The results of the examination showed that although no coloration was observed on Specimens No. 1 and No. 2 of Examples 1 and 2, a coloration was
5 observed on Specimen No. 4 of Comparative Example 2. Since Specimen No. 3 showed a blue colour before immersing into the solution of the dye-stuff, it could not be compared. From these results it was clear that the ceramic material of the present invention differs from the
10 known ceramic material.

EXAMPLE 4

Twenty grams of the aggregate of hydroxyapatite of the present invention obtained in Example 1, Specimen No. 1, were fired at a temperature of 1250°C under a
15 reduced pressure of 10^{-2} mmHg for one hour, and cooled to 200°C under the reduced pressure to prepare a ceramic material. The thus prepared ceramic material was white in colour, transparent and showed a density of 3.16 g/cm³.

EXAMPLE 5

A sintering test was carried out on the aggregates of hydroxyapatite of Specimen No. 1 of Example 1 and Specimen No. 4 of Comparative Example 2. 20 g samples of each Specimen were baked at each temperature
25 of 1200, 1250, 1300 and 1350°C for one hour, and the amount of whitlockite formed within the fired material was determined by X-ray diffraction analysis. The results are shown in Table 3. As is seen in Table 3, the difference between the ceramic material according
30 to the present invention and the known ceramic material is clear.

EXAMPLE 6

The ceramic material prepared in Example 3 from Specimen No. 1 was pulverized and the fraction
35 passed through a sieve of 200 mesh (aperture 74 microns)

- 18 -

was collected. The thus collected powder was mixed with a 6 : 4 by weight mixture of copolymer of bisphenol A and glycidyl methacrylate and monomeric methyl methacrylate at a volume ratio (calculated by the respective weights and densities of both components) of 1 : 1, and after the further addition of 0.05% by weight of benzoyl peroxide as a polymerization initiator, the mixture was mixed to be uniform, and after pouring into a glass tube of 5 mm inner diameter and debubbling, a polymerization was carried out at 80°C for 2 hours on the mixture to obtain a composition of hydroxyapatite. After processing the composition into a cylinder of 3.5 mm in diameter and 10 mm in length, it was implanted into the drilled hole of the jaw-bone of an adult dog just after a tooth extraction. The implant was not naturally removed even after 3 months of implantation. After 6 months of implantation, the jaw-bone of the dog was cut off to be examined by an optical microscope and roentgenography. It was found that the implanted part had healed normally and new bone-tissue had formed in the gap between the implant and the jaw-bone.

Table 1: Properties of Aggregates of hydroxyapatite

Classification	Specimen No.	Reaction time(hour) temp. (°C)	Yield (%)	Elementary analysis			Size of crystal		Pore volume ¹⁾ (ml/g)	Pore- ²⁾ radius (Å)
				Ca(%)	P(%)	Ca/P	length L(Å)	width W(Å)		
Theoretical				39.89	18.43	1.67				
Present invention	1	48 20	99	39.75	18.43	1.67	300	80	0.47	100
	2	24 40	99	39.80	18.46	1.67	900	200	0.65	140
Comparative	3	24 70	99	39.78	18.45	1.67	2300	350	0.88	400
	4	24 20	98	39.50	18.40	1.66	200	200	0.45	90

Note: 1) and 2) determined by POROSIMETRO Model 70 (manufactured by Acom Co.)

Table 2: Properties of Hydroxyapatite Ceramic Materials

Classification	Raw material Specimen No.	Elementary analysis			Mean size of crystal (micron)	Density (g/cm ³)	Colour	Thermal stability 1)
		Ca(%)	P(%)	Ca/P				
Theoretical		39.89	18.43	1.67				
Present invention	1	39.87	18.51	1.67	11	3.16	white translucent	no decomposition
	2	39.86	18.48	1.67	5	3.15	white translucent	no decomposition
Comparative example	3	39.85	18.47	1.67	2.5	3.02	light blue	no decomposition
	4	38.34	18.40	1.61	3	3.12	white	decomposition observed

Note: 1) evaluated by the presence or absence of the formation of whitlockite in the specimen heated for one hour at a temperature of 1,350°C.

Table 3: Results of Sintering Test: amount of whitlockite

Unit (%)

Classification Raw Material	Temperature of firing (°C)		
	1200	1250	1300
Present invention Specimen No. 1	0	0	0
Comparative example Specimen No. 4	6.0	41.5	41
			42

- 21 -

C L A I M S

1. A process for preparing hydroxyapatite by the reaction of calcium hydroxide with phosphoric acid, characterised by

(a) converting calcium carbonate powder into calcium oxide by thermal decomposition in an inert atmosphere at a temperature of 800 to 1300°C for 0.5 to 10 hours;

(b) cooling the calcium oxide to a temperature lower than 500°C in the inert atmosphere;

(c) slaking the cooled calcium oxide with water while agitating thereby to obtain calcium hydroxide; and

(d) reacting the calcium hydroxide with an aqueous solution of phosphoric acid while agitating in an inert atmosphere thereby to obtain hydroxyapatite.

2. A process according to claim 1, characterised in that an aqueous suspension of calcium hydroxide is reacted with the aqueous solution of phosphoric acid in step (d).

3. A process according to claim 1 or 2, characterised in that the calcium hydroxide is reacted with the aqueous solution of phosphoric acid in step (d) at a temperature of 0 to 50°C.

4. A process according to claim 1, 2 or 3 characterised in that the reaction product from step (d) is filtered and dried to a water content of 2% by weight or less.

5. A filtered, dried cake of synthetic hydroxyapatite characterised by having a three-dimensional porous structure with an average pore radius of 50 to 150 Å and a pore volume of 0.2 to 0.8 cm³/g, said cake

- 22 -

comprising crystalline hydroxyapatite having an atomic ratio of calcium to phosphorus of 1.67 : 1 to 1.69 : 1 in which the crystals have a length of 150 to 1200 Å, a width of 50 to 400 Å, and a length to width ratio of 3:1 to 10:1.

6. A ceramic material comprising synthetic hydroxyapatite and having an atomic ratio of calcium to phosphorus of 1.67 : 1 to 1.69 : 1 characterised by average crystal size of 4 to 20 μ , a density of 3.14 to 3.16 g/cm³ and a thermal stability such that substantially no whitlockite is formed upon heating for at least one hour at a temperature of 1350°C, said ceramic material being colourless or semi-transparent.

7. A ceramic material according to claim 6 characterised by comprising the sintered product of a dried, filtered cake as claimed in claim 5.

8. An implant material comprising a ceramic hydroxyapatite material and a biologically acceptable bonding material characterised in that the ceramic material is as claimed in claim 6 or 7.

9. An implant material according to claim 8, characterised in that the ceramic material forms from 5 to 70% of the surface area of the implant material.

10. An implant material according to claim 8 or 9, characterised in that the bonding material comprises at least one of polycondensates of bisphenol A and glycidyl methacrylate, methyl methacrylate polymers, 2-hydroxyethyl methacrylate polymers, triethyleneglycol dimethacrylate polymers, ethylene polymers, sulfone polymers, polyamides, polyesters, tetrafluoroethylene polymers, vinylidene fluoride polymers and polycarbonates.